REMARKS

In order to further Applicants' business interests and the prosecution of the Application yet without acquiescing to the Examiner's arguments and while reserving the right to file the original or similar claims in the future, Applicants herein amend claim 79 and cancel claims 80, 82 and 94. Support for amended claim 79 can be found throughout the Specification and claims as originally filed, for example, in original claim 4; paragraph 76 of published Application (PCT Pub. 2002/0006406), Example 5, among other places. No new matter has been added.

As such, Claims 79, 81, 83-84, 86-89, and 92-93 are currently pending.

I. The Claims are Enabled and Supported by Adequate Written Description

The Examiner rejected Claims 82 and 94 under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the invention was filed, had possession of the claimed invention (Office Action pages 3). Applicants respectfully disagree. Nonetheless, in order to further Applicants' business interests and the prosecution of the Application yet without acquiescing to the Examiner's arguments and while reserving the right to file the original or similar claims in the future, Applicants have cancelled claims 82 and 94. Applicants respectfully submit that the rejection under 35 U.S.C. 112, first paragraph has been rendered moot.

II. The Claims are Not Obvious

The Examiner rejected Claims 79-84, 86-89, and 92-94 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Zygmunt, Goldberg and Stark, and further in view of Oldham. Applicants respectfully disagree.

The Examiner states "Applicant's arguments have been considered but were not deemed persuasive, and have been already addressed on multiple occasions in the preceding Office actions and/or in the Board decision. The rejection in maintained." (Office Action, page 15).

Applicants respectfully assert that this statement is incorrect. Specifically, Applicants respectfully assert that the Examiner failed to address each and every one of Applicants' arguments presented in Applicants' response filed 01 March 2010. In particular, the Examiner failed to address and accord proper weight to Applicants' assertion that the claimed dosage had not been recognized by the art to attain or provide a recognizably beneficial result. Furthermore, the claimed range provides unexpected benefits not achieved or suggested by the cited references, and furthermore, because the cited references failed to appreciate the importance of the claimed range, the cited references actually teach away from the claimed dosage of the invention.

I. The Cited References Fail to Recognize and Therefore Fail to Teach or Suggest the Claimed Range As A Result Effective Variable

The Examiner alleges that Zygmut teaches lysostaphin dosages in the range of 0.5 to 50 mg/kg, or multiple doses in the range of 0.5 to 50 mg/kg (Office Action, page 4). The Examiner further alleges that it would have been obvious to select the claimed dosage of 3-25 mg/kg because it is a result-effective variable, within the range taught by Zygmut, which may be optimized by an artisan in the course of routine optimization (Office Action, page 4).

Applicants respectfully disagree with the Examiner's allegation that the claimed dosage is a result-effective variable.

Specifically, Applicants assert that the claimed dosage, prior to the discoveries made during development of embodiments of the invention, had not been recognized by the art to attain or provide a recognizably beneficial result. Moreover, the claimed range provides unexpected benefits not achieved or suggested by the cited references, and as described below, the cited references teach an ordinary artisan to avoid the claimed dosage of the invention.

A particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation. *In re Antonie,* 559 F.2d 618, 621 (CCPA 1977); *In re Boesch,* 617 F.2d 272, 276 (CCPA 1980)("[D]iscovery of an optimum value of a result effective variable … is ordinarily within the skill of the art."); *see also In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003) ("The normal desire of scientists or artisans to improve upon what is already generally known provides the

motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages.").

Thus, Aller stands for the principle that the discovery of an optimum value of a variable in a known process is normally obvious. *In re Antonie*, 559 F.2d 618, 620, 195 USPQ 6, 8-9 (CCPA 1977). Exceptions to this general rule lie in cases where the results of optimizing a variable, which was known to be result effective, were unexpectedly good or where the parameter optimized was not recognized to be a result-effective variable. Id.

Applicants respectfully assert that experiments conducted during development of embodiments of the invention permitted Applicants to recognize, for the first time, a method of treating a subject with a staphylococcal infection of an organ with a dose of 3-25 mg/kg/day of the type claimed to be a result-effective variable bearing on the ability to result in a 3 fold or greater reduction in Staphylococcus burden. There is nothing in Zygmut, considered alone or in any combination with Goldberg, Stark or Oldham, which demonstrates that this recognition was shared by the prior art. In other words, the applied references do not establish that a dose of lysostaphin of 3-25 mg/kg/day to a human subject harboring a staphylococcal infection of an organ was an art-recognized result-effective variable. Applicants respectfully assert that this fact situation falls into one of the exceptions to the general rule established by Aller, and for this reason alone, the claims are not obvious. Moreover, the cited references teach an ordinary artisan to avoid the claimed dosage of the invention

II. The Cited References Lead One of Ordinary Skill in the Art Away From the Claimed Invention

Applicants respectfully assert that the administration of dosages within the claimed range (e.g., to dogs 7 and 10 in Goldberg) of the prior art did not effectively treat infection of organs in the subjects and also lead to relapse in the subjects. Therefore, one of ordinary skill in the art would have had to proceed contrary to the teachings of Goldberg to arrive at the claimed invention. Thus, in order to arrive at the claimed invention, one of ordinary skill in the art would have had to employ dosages shown in Goldberg to result not only in relapse of infection, but also in the appearance of high levels of resistant strains.

Accordingly, Applicants respectfully assert that the cited references clearly direct one of ordinary skill in the art away from the claimed invention. In particular, one of ordinary skill in

the art would understand Goldberg, and Zygmunt summarizing the same, to teach the use of higher doses (e.g., 50 mg/kg/day or more) that provide results that were not achievable with lower dosages of the claimed invention. Goldberg did not suggest the utility of a method of treating a staphylococcal infection of an organ in a human subject, comprising: providing a subject comprising a staphylococcal infection, wherein the infection comprises infection of an organ; and administering to the subject a recombinantly produced lysostaphin in a dose of 3-25 mg/kg/day, wherein the administering results in a 3-fold or greater reduction of staphylococci present in the subject. In fact, Goldberg teaches the avoidance of methods of treatment recited in the claims. In particular, the ordinarily skilled person, following the teachings of Goldberg, would have been forced to select a dosage regimen for lysostaphin characterized by high dose (e.g., at least 50 mg/kg/day), and not a dose of the claimed invention (e.g., as recited in Claims 79, 94, and claims dependent thereon).

According to the MPEP, a *prima facie* case of obviousness may be rebutted by showing that the art, in any material respect, teaches away from the claimed invention. *In re Geisler*, 116F.3d 1465, 1471, 43 USPQ3d 1362, 1366 (Fed. Cir. 1997). MPEP §2144.05(III). Moreover, a prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984) (See MPEP §2141.02). Rebuttal evidence may also include evidence that the claimed invention yields unexpectedly improved properties or properties not present in the prior art. Rebuttal evidence may consist of a showing that the claimed compound possesses unexpected properties. *Dillon*, 919 F.2d at 692-93, 16 USPQ2d at 1901. A showing of unexpected results must be based on evidence, not argument or speculation. *In re Mayne*, 104 F.3d 1339, 1343-44, 41 USPQ2d 1451, 1455-56 (Fed. Cir. 1997).

Although Applicants do not believe a *prima facie* case of obviousness has been established, a *prima facie* case of obviousness based on overlapping ranges can be rebutted by showing the criticality of the claimed range. "The law is replete with cases in which the difference between the claimed invention and the prior art is some range or other variable within the claims. . . . In such a situation, the applicant must show that the particular range is critical, generally by showing that the claimed range achieves **unexpected results** relative to the prior art range." *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990).

Any differences between the claimed invention and the prior art may be expected to result in some differences in properties. The issue is whether the properties differ to such an extent that the difference is really unexpected. *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Unexpected results for a claimed range as compared with the range disclosed in the prior art have been shown by a demonstration of a marked improvement over the art, as to be classified as a difference in kind, rather than one of degree." *In re Waymouth*, 499 F.2d 1273, 1276, 182 USPQ 290, 293 (CCPA 1974).

Goldbergh teaches that administration of dosages between 3-25 mg/kg/day **did not** achieve the same result as administration of higher doses (e.g., 50 mg/kg/day). Specifically, dogs administered lower dosages in the claimed range displayed an increase in lysostaphin resistant strains and also relapse, two highly unfavorable outcomes.

> "The largest proportions of isolates found to be resistant were in three dogs receiving small repeated doses. The emergence of resistant isolates in these dogs may have resulted from repeated exposure to small amounts of enzyme. These three dogs relapsed, perhaps as a result of the large proportion of resistant staphylococci, or perhaps because the small doses of enzyme were insufficient to control the infection." (Goldberg, page 52, left column, beginning at second full paragraph).

The claims recite treating a methicillin-resistant staphylococcal infection of an organ by administering lysostaphin in a dose of 3-25 mg/kg/day. Experiments performed during development of embodiments of the invention demonstrate the effectiveness of such treatment:

> "As shown in table 6, a regimen of 5mg/kg lysostaphin three times daily was the most efficacious treatment. An impressive statistic is that this treatment completely sterilizied the heart valve vegetation in all but one of the rabbits. This was far superior to the standard regimen used as a positive control in this infection model: 30 mg/kg vancomycin twice daily. A regimen of 5 mg/kg lysostaphin once daily was less efficacious than the thrice daily regimen, but was almost as good as vancomycin in reducing bacterial counts in the vegetation; in fact, the effect was not statistically different from the vancomycin group." (Specification, page 20, lines 18-28, see also Table 6).

Results achieved by the claimed invention stand in stark contrast to the teaching of Goldbergh that dosages between 3-25 mg/kg/day did not achieve the same result as administration of higher doses resulted in the emergence of resistant isolates, and were

insufficient to control infection. The results achieved by the claimed treatment represent a "difference in kind," rather than one of degree, and are therefore unexpected results for the claimed range as compared with the range disclosed by Goldbergh. *In re Waymouth*, 499 F.2d 1273, 1276, 182 USPQ 290, 293 (CCPA 1974). The claimed treatment provides unexpected results and therefore rebuts the *prima facie* case of obviousness alleged by the Examiner.

Previous work with lysostaphin in established organ infections showed limited reduction of bacterial load in a kidney mouse model, and in heart valves and other organs in a dog endocarditis model, at doses ranging from 50 to 250 mg/kg/treatment (Specification, paragraphs 0008-0010). Despite the significantly higher dosages used in these studies, effectiveness of the magnitude required in the treatment of organ infections was not observed. The results of the cited references do not allow an ordinary artisan the ability to predict that the methods of the claimed invention would lead to rapid, total sterilization of virtually all heart valve vegetations, as was demonstrated using the doses of lysostaphin of the claimed invention. The claimed methods provide heretofore unachieved and unexpected results and therefore rebut the *prima facie* case of obviousness alleged by the Examiner.

Applicants respectfully assert that the Examiner has failed to establish a *prima facie* case of obviousness. To the extent the Examiner has established such a case, Applicants assert that the *prima facie* case of obviousness is rebutted by unexpected results of the claimed invention, and by a showing that the art teaches away from the claimed invention. Accordingly, Applicants respectfully request that the rejection of the Claims under 35 U.S.C. §103(a) be withdrawn.

CONCLUSION

For the reasons set forth above, it is respectfully submitted that Applicants have addressed all grounds for rejection and Applicants' claims should be passed to allowance. Reconsideration of the application is respectfully requested. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourage the Examiner to call the undersigned collect at (608) 662-1277.

Respectfully submitted,

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